IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	**PENN-0065**
Inventors:	**Wolfe and Fraser**
Serial No.:	**08/393,066**
Filing Date:	**February 23, 1995**
Examiner:	**D. Crouch**
Group Art Unit:	**1804**
Title:	**Methods of Delivering Genes to the Central Nervous System of a Mammal**

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Declaration of Laura M. Plunkett, Ph.D.

I, Laura M. Plunkett, hereby declare that:

1. I received a Bachelor's degree in Zoology from the University of Georgia and a Doctorate in Pharmacology from the University of Georgia, College of Pharmacy. I received a postdoctoral fellowship from the National Institute of General Medical Sciences, the Pharmacology Research Associate Training Program (PRAT Program), and performed my postdoctoral work at the National Institute of Mental Health. I am currently a manager in the Health Sciences group at ENVIRON International Corporation. Prior to joining ENVIRON, I was an Assistant Professor of Pharmacology in the Department of Pharmacology, College of Medicine, at the University of Arkansas for Medical Sciences. I also held an adjunct appointment to the Division of Toxicology. During my postdoctoral training and my years in academics, I performed basic research in pharmacology; my areas of expertise were cardiovascular and neuropharmacology, with an emphasis in

neuropeptides and the neurochemical mechanisms involved in autonomic nervous system function. I also worked closely with a colleague who is a pharmacokineticist and have several publications relating to drug disposition. During my five years with ENVIRON, my consulting work has focused on U.S. Food and Drug Administration (FDA) regulation of drugs, biologics, and medical devices. I have assisted many clients in navigating the FDA approval process and am currently developing my own practice in Houston, Texas that emphasizes providing technical and regulatory support to small to medium-sized biotechnology companies. I have experience with both chemically-synthesized drug products as well as products of biotechnology. I consider myself an expert in pharmacology and toxicology and the FDA regulation of drug products of all types, regardless of the chemical nature of the substance. The details of my experience and a list of my publications are in my Curriculum Vitae that is attached as Exhibit 1.

2. I was asked by Dr. Jane Licata to assist her in the preparation of her response to the Patent Examiner concerning the method of delivering genes to the central nervous system of a mammal. She provided me with the specification as well as the Examiner's response dated September 13, 1996.

3. In order to demonstrate therapeutic utility it is necessary to demonstrate a pharmacological effect. By definition, a pharmacological effect is an effect of a drug or chemical agent that affects living processes (as defined in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, Section 1; Exhibit 2). Delivery of a gene to cells in the central nervous system (CNS) and subsequent expression of those genes is part of a living process, and, therefore, a pharmacological effect, just as

hormone release induced by a drug would be a pharmacologic effect. Therefore, the data described in the specification are demonstrative of therapeutic utility.

The fact that the specification describes a novel delivery system for a gene is an important consideration for the pharmacologist. This is because a therapy cannot be successful unless the target cells in the body are reached and effectively altered. Using the data described in the specification in Examples 4 and 5 (pages 25-26 of the specification), one of skill would have assurance that the invention would result in delivery of a gene to the target cells, the CNS, and be followed by expression of the gene in these target cells.

Further, the fact that the specification describes an experiment in animals in Examples 4 and 5 where the viral vector was administered through corneal abrasion indicates to one of skill that other peripheral routes of administration (intravenous injection for example) would also be suitable. This is because fundamental principles of pharmacokinetics indicate that although the rate and extent of absorption may be affected by route of administration, all routes will result in levels of the administered substance appearing in the systemic circulation and thus available for pharmacologic activity (*Goodman and Gilman's The Pharmacological Basis of Therapeutics* , pp. 5-11; Exhibit 3). Corneal abrasion is simply one route of peripheral administration.

4. It is a fundamental principle that pharmacological effect data are directly applicable to a demonstration of therapeutic utility. Such data are routinely requested and accepted by the FDA. If a substance shows good pharmacological activity *in vivo*

in animals, these data can be used for choosing a dosing strategy in humans. This is all part of the standard drug development process, has been so for two decades, and is not a novel concept. The information contained in the specification provides such data that would be used, in conjunction with general knowledge about the physiological system to be manipulated, to establish a strategy for use of such a delivery system in humans.

Finally, there is an important difference between therapeutic utility and therapeutic effect or benefit. *In vivo* animal data provide information on utility. The therapeutic effect or benefit of a treatment strategy, however, is the standard applied in the drug approval process which is handled by the FDA.

5. The Examiner asserts that the data described in a paper by Dobson et al. (1989) teaches delivery of a gene to the CNS of mice. Careful review of this paper, however, demonstrates that the authors describe only <u>peripheral</u> nervous system delivery. The spinal ganglia that are shown to have taken up the viral vector are actually located outside the CNS (Figure 5 in Dobson et al. 1989). The CNS is comprised exclusively of the brain and spinal cord. Spinal ganglia are located outside the CNS (see discussion in Landsberg, L. And J.B. Young, 1994, *Harrison's Principles of Internal Medicine*, pp. 412-413; Exhibit 4). The CNS is protected from exposure to foreign compounds (such as viruses) by the blood-brain barrier, a series of tight junctions at capillaries within the CNS (pg. 487 in *Harrison's Principles of Internal Medicine*; Exhibit 5). Therefore, in order for an agent to enter the CNS after injection into the peripheral system, it must be able to cross this barrier. Many therapeutic agents cannot cross this barrier and as a result are ineffective for treating clinical conditions that are caused by pertubations

in CNS function.

As a result, the fact that someone has shown the ability of a viral vector to infect cells in the peripheral nervous system (as in Dobson et al. 1989) would not imply to one of skill that that same vector would infect and successfully express genes in cells of the CNS. A pharmacologist would be convinced by data such as is seen in the specification (Examples 4 and 5) that the subject of the invention is capable of CNS infection and successful gene expression in a mammal.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information or belief are believed to be true: and further that those statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing thereupon, or any patent to which this verified statement is directed.

12/12/96
Date

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